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Tislelizumab synergizes with surgery to augment the survival benefit in stage II-III non-small cell lung cancer

Xuhua Huang[1] · Linhai Zhu[1] · Jiacong Liu[1] · Yanye Wang[1] · Yiqing Wang[1] · Pinghui Xia[1] · Wang Lv[1] · Jian Hu[1,2]

Abstract
Objectives This retrospective study evaluated the individual benefits of tislelizumab and surgery, as well as their synergistic effect on progression-free survival (PFS) and overall survival (OS) of stage II-III non-small cell lung cancer (NSCLC) patients.
Methods From September 2019 to June 2022, all participants with potentially resectable NSCLC who received chemotherapy (C) or tislelizumab plus chemotherapy (T) were included in the study. Participants were categorized into four groups based on surgery or not (S or NS) and the utilization of tislelizumab (T or C). Progression-free survival (PFS) and overall survival (OS) were evaluated using the Kaplan–Meier method and log-rank test, as well as Cox proportional hazards models.
Results Compared to C, T was associated with significantly higher objective response rate (64.54% vs. 34.78%, p = 0.003), higher pathological complete response rate (40.00% vs. 14.06%, p = 0.007), and higher major pathological response rate (60.00% vs. 20.31%, p < 0.001). The T + S group exhibited a proportionately higher reduction in the risk of disease progression or death compared to the sum of the T + NS group and C + S group. Regardless of C or T, surgery was associated with improved OS (p < 0.01). Without surgery, T did not show significant improvement in PFS or OS. However, with surgery, T significantly improved both PFS and OS (ps < 0.01).
Conclusion Tislelizumab with subsequent surgery synergistically improves the survival benefits in patients with NSCLC.
Keywords Tislelizumab · Surgery · Progression-free survival · Overall survival · Non-small cell lung cancer

1 Introduction

Non-small cell lung cancer (NSCLC) accounts for a significant proportion of cancer-related mortalities worldwide [1]. For patients with TNM stage II-III NSCLC, 5 year overall survival rates were less than 52% and 36%, respectively [2].

A multimodal treatment approach, including surgery and perioperative therapies, is often employed to improve overall survival rates. Recently, immunotherapy has emerged as a promising therapeutic strategy in various malignancies, with immune checkpoint inhibitors showing remarkable efficacy in potential resectable NSCLC [3, 4].

Tislelizumab, a novel anti-PD-1 monoclonal antibody developed by BeiGene (Beijing, China) [5], has demonstrated a notable safety profile [6, 7] and has been identified as an effective first-line or second-line treatment for advanced NSCLC based on the RATIONALE study series [8, 9]. Additionally, in resectable malignancies like esophageal squamous cell carcinoma and others, preoperative tislelizumab plus chemotherapy brought high major pathological remission (MPR) rate, pathological complete remission (pCR) rate, and R0 resection rate [10–12]. However, its potential additive or even synergistic effects with surgical resection in earlier stages of NSCLC remain less explored.

Furthermore, despite the absence of direct comparative clinical trials, systematic reviews and meta-analyses comparing tislelizumab plus chemotherapy and other immunochemotherapy regimens (such as pembrolizumab) showed that tislelizumab plus chemotherapy exhibit comparable progression-free survival and safety in locally advanced or metastatic NSCLC [13]. Additionally, in the context of the Chinese healthcare landscape, the treatment cost associated with tislelizumab is considerably lower than that of pembrolizumab [14]. Therefore, in the first-line treatment of NSCLC, tislelizumab may emerge as an alternative option.

In this context, investigating the combination of tislelizumab with surgery for stage II-III NSCLC holds great clinical significance. This study aims to explore whether the integration of tislelizumab into the classical standard treatment paradigm could lead to improved survival outcomes for patients with stage II-III NSCLC. By elucidating the potential additive effects of tislelizumab and surgery, this study seeks to provide valuable insights into optimizing treatment strategies and ultimately improving the overall survival of stage II-III NSCLC patients.

2 Methods

2.1 Ethics statement

This study was approved by the First Affiliated Hospital of Zhejiang University School of Medicine (FAHZU) (Grant No. 2021IIT No. 844) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before all the treatments.

2.2 Study participants

This retrospective study identified all stage II-III NSCLC patients who underwent tislelizumab plus platinum-based dual-drug chemotherapy (T) or received platinum-based dual-drug chemotherapy alone (C) from the patient cohort at the Department of Thoracic Surgery, FAHZU. Comprehensive patient data, encompassing demographic and clinical information, laboratory findings, imaging data, and surgical details gathered from the hospital's electronic medical record system were recorded in pre-designed tables.

The inclusion criteria were as follows: (1) age of 18 years or older; (2) histopathological confirmation of NSCLC before medication; (3) TNM stage II or III; (4) Eastern Cooperative Oncology Group—Performance Status (ECOG-PS) score < 2; (5) receipt of tislelizumab plus chemotherapy or chemotherapy alone; (6) upon initial consultation, the medical team assessed the mass to ascertain its potential resectability or the probability of benefiting from preoperative medication.

The exclusion criteria were as follows: (1) participants who lacked pre-medication chest imaging data, including computed tomography (CT) or positron emission tomography-computed tomography (PET-CT), or those who had only one imaging data throughout the entire follow-up period in the hospital's system; (2) patients who had previously undergone radiotherapy, interventional therapy, targeted therapy, other forms of immunotherapy, or surgery; (3) individuals who had previously undergone genetic testing that identified gene mutations potentially targeted by targeted therapy, including EGFR, KRAS, NRAS, BRAF, HER-2, MET, PIK3CA, ALK, ROS1, and RET; (4) patients with active pulmonary tuberculosis, hepatitis C, or autoimmune diseases; (5) patients with severe ventilatory disorders or significant gas exchange defects; (6) individuals who were immunosuppressed or immunodeficient, such as those receiving steroid therapy or diagnosed with HIV infection; (7) patients who exhibited allergies or intolerance to any component of tislelizumab or chemotherapy drugs; (8) participants involved in other concurrent clinical trials.

The follow-up period is extended for a minimum of one year after the administration of treatment. Progression-free survival (PFS) was defined as the duration from the initiation of treatment until the occurrence of disease progression

or mortality due to any cause. Overall survival (OS) was defined as the duration from the initiation of treatment to the date of death resulting from any cause.

2.3 Treatment procedures

The enrolled patients in this study underwent intravenous administration of tislelizumab (200 mg) plus chemotherapy or chemotherapy alone for 2–4 cycles before proceeding to assessment about surgical resection. Each treatment cycle lasts about 3 weeks, and the chemotherapy regimens employed consisted of platinum-based dual-drug combinations. Specifically, patients diagnosed with histopathologically confirmed lung squamous cell carcinoma (LUSC) received nab-paclitaxel (260 mg/m^2) plus carboplatin (AUC = 5), whereas those with lung adenocarcinoma (LUAD) were administered pemetrexed (500 mg/m^2) plus carboplatin (AUC = 5). Considering the relevantly advanced tumor staging, individual variations in treatment responsiveness, and the non-standardized nature of the combined immunotherapy and surgical protocols, the selection of each patient's treatment plan was jointly determined by the surgeons and the patients themselves. Generally, patients who undergo surgery continue with preoperative treatment until completion of a 6-cycle regimen, followed by regular follow-up. For patients who were not eligible for surgery, a recommendation was made for subsequent treatment with radiotherapy plus chemotherapy, along with regular follow-up.

2.4 Tumor response evaluation

The patients underwent chest CT scans every 2 cycles before surgical resection assessment. Tumor staging was assessed utilizing the 8th edition of the American Joint Committee on Cancer TNM staging system [15] at baseline. Tumor treatment response in the target lesions was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [16]. Complete response (CR) was defined as the complete disappearance of all target lesions, while partial remission (PR) was defined as a minimum 30% reduction in the overall diameter of the target lesions. Stable disease (SD) was characterized by a change in the target lesion size between -30% and 20% without the formation of new lesions, whereas progressive disease (PD) was defined as a 20% or greater increase in the overall diameter of target lesions or the emergence of new lesions.

2.5 Treatment-related adverse events evaluation

The investigation utilized the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to evaluate adverse events (AEs). Blood routine tests and serum biochemical tests were routinely conducted to evaluate potential blood system disorders, endocrine disorders, hepatic function, and renal function abnormalities. Additionally, patients' self-reported complaints were carefully considered to evaluate occurrences of gastrointestinal reactions, sensory neural disorders, and skin reactions.

2.6 Surgical treatment procedures

Within 4–6 weeks following the completion of preoperative therapy, patients were subjected to a thorough reevaluation by the medical team to ascertain their eligibility for surgical intervention. The surgical procedures employed in this study encompassed open surgery and video-assisted thoracoscopic surgery (VATS), including lung wedge resection, lung lobectomy, lung sleeve resection, pneumonectomy, and thoracal exploration, all of which were accompanied by standardized lymph node dissection or sampling. While the preoperative CT images served as the basis for the initial surgical approach, modifications were introduced during the surgical procedure as dictated by pertinent factors, such as the presence of dense adhesions or complex anatomical structures.

2.7 Pathological reaffirmation

Pathological data, including pathological type, degree of differentiation, depth of invasion, resection margin, lymph node metastasis, and tumor regression grade, were extracted by two independent investigators. Pathological complete response (pCR) was defined as the absence of cancer cells, determined by assessing the proportion of remaining viable tumor cells in the original lesion area. Major pathological response (MPR) was defined as the presence of less than 10% residual viable cancer cells.

2.8 Statistical analysis

The sample size was determined using the module for log-rank tests in the Power Analysis and Sample Size (PASS) software (version 15.0.5). Despite the categorization into four groups, previous data regarding survival comparisons between neoadjuvant immunochemotherapy and neoadjuvant chemotherapy followed by surgery was applied for sample size estimation [17]. The specified parameters included a hazard ratio for survival of 0.55, accrual time of 3 years, total time of 4 years, a two-sided test at a significance level of $P = 0.05$, a desired statistical power of 0.80, and equal participant allocation for groups. With these specifications, PASS indicated that at least 112 participants in total were required.

Continuous variables following normal distribution were presented as mean (standard deviations) while variables with non-normally distributed data were presented as median (ranges), and categorical variables were presented as frequencies (percentages). Measures of analysis of variance, Student's t-test, Chi-squared test, and independent samples Kruskal–Wallis test were performed to examine the demographical and clinical differences after surgery / tislelizumab stratification. Significant group effects were further evaluated with Bonferroni-adjusted or Dunnett-adjusted pairwise comparisons.

Cox proportional hazards models were computed to examine the groups' independent and interactive effects for PFS and OS, adjusting for significant demographical and clinical covariates. Significant group effects were further evaluated with Bonferroni-adjusted log-rank pairwise comparisons. Kaplan–Meier curves with the log-rank test were applied for survival analysis. Two-tailed p-value < 0.05 was considered statistically significant. Statistical analysis was performed using R 4.2.1.

3 Results

3.1 Better clinical and pathological response of tislelizumab

A total of 154 participants were included in this study. After stratification, there were 25 (16.23%) T + S participants, 14 (9.09%) T + NS participants, 64 (41.56%) C + S participants, and 51 (33.12%) C + NS participants. Group differences in demographic and clinical characteristics at baseline are summarized in Table 1. Age, pulmonary comorbidities, pathological subtypes, and treatment cycle number significantly differed among groups (ps < 0.05).

The clinical and pathological responses of T group and C group are summarized in Table 2 and Table 3. Before surgery, tislelizumab plus chemotherapy was associated with a significantly higher ORR than chemotherapy alone (61.54% vs. 34.78%, p = 0.003). After surgery, tislelizumab plus chemotherapy showed a significantly superior pathological response than chemotherapy alone (p < 0.001). A significantly better pCR rate (40.00% vs. 14.06%, p = 0.007) and better MPR rate (60.00% vs. 20.31%, p < 0.001) were observed in the T + S group than in the C + S group. Specifically, the T group was associated with significantly fewer adverse events including leukocyte suppression, anemia, constipation, liver damage, and skin reaction (all ps < 0.05) (Supplementary Table 1), and less estimated blood loss during surgery (p = 0.011) (Supplementary Table 2).

3.2 Synergistic effect of tislelizumab and surgery on survival

The median follow-up time of the whole cohort was 658 days (range: 101—2346 days). Considering the independent effect and interactive effect of tislelizumab treatment and surgery, the Cox regression model was applied and a significant interaction was found between tislelizumab treatment and surgery for PFS (B = -0.248, p for interaction = 0.036) and OS (B = -0.363, p for interaction = 0.004). After adjusting for age, pulmonary comorbidities, pathological subtypes, and number of treatment cycles in the Cox proportional hazards model, the PFS and OS results stratified by surgery and the utilization of tislelizumab are summarized in Table 4 and Fig. 1.

Compared to the C + NS group, tislelizumab reduced about 33.2% risk of disease progression (HR = 0.668, p = 0.335) and about 8.8% risk of death (HR = 0.912, p = 0.848) for trend, while surgery reduced about 8.8% risk of disease progression (HR = 0.632, p = 0.069) and about 46.7% risk of death (HR = 0.533, p = 0.018). However, the T + S group was significantly associated with an 87.1% reduced risk of disease progression (HR = 0.129 [95%CI: 0.045–0.373],

Table 1 Participant characteristics at baseline

Characteristic	All (n = 154)	T + S (n = 25)	T + NS (n = 14)	C + S (n = 64)	C + NS (n = 51)	Test value	P-value
Age, mean (SD)	64.23 (7.79)	66.88 (4.49) [a]	71.36 (8.40) [c]	61.63 (8.11)[a,c]	64.24 (6.94)	8.302	< 0.001
Gender (Male), n (%)	132 (85.71)	24 (96.00)	13 (92.86)	55 (85.94)	40 (78.43)	4.955	0.175
ECOG-PS (= 0), n (%)	97 (62.99)	15 (60.00)	10 (71.43)	41 (64.06)	31 (60.78)	0.661	0.882
Smoking status (Yes), n (%)	101 (65.58)	18 (72.00)	7 (50.00)	40 (62.50)	36 (70.59)	2.654	0.448
Drinking status (Yes), n (%)	56 (36.36)	10 (40.00)	6 (42.86)	23 (35.94)	17 (33.33)	0.605	0.895
Comorbidities, n (%)							
Pulmonary disease	22 (14.29)	8 (32.00) [b]	4 (28.57)	7 (10.94)	3 (5.88) [b]	12.267	0.007
Cardiac disease	15 (9.74)	4 (16.00)	3 (21.43)	4 (6.25)	4 (7.84)	4.385	0.223
Diabetes mellitus	15 (9.74)	1 (4.00)	0 (0.00)	5 (7.81)	9 (17.65)	6.345	0.096
Hypertension	53 (34.42)	12 (48.00)	5 (35.71)	19 (29.69)	17 (33.33)	2.715	0.438
Pathology, n (%)						7.956	0.047
LUSC	110 (71.43)	21 (84.00)	13 (92.86)	45 (70.31)	31 (60.78)		
LUAD	44 (28.57)	4 (16.00)	1 (7.14)	19 (29.69)	20 (39.22)		
Tumor location, n (%)						20.016	0.520
Superior lobe of left lung	42 (27.27)	8 (32.00)	3 (21.43)	14 (21.88)	17 (33.33)		
Inferior lobe of left lung	26 (16.88)	3 (12.00)	3 (21.43)	13 (20.31)	7 (13.73)		
Superior lobe of right lung	37 (24.03)	7 (28.00)	3 (21.43)	14 (21.88)	13 (25.49)		
Middle lobe of right lung	7 (4.55)	1 (4.00)	0 (0.00)	3 (4.69)	3 (5.88)		
Inferior lobe of right lung	28 (18.18)	3 (12.00)	3 (21.43)	18 (28.13)	4 (7.84)		
Hilum of left lung	9 (5.84)	2 (8.00)	2 (14.29)	1 (1.56)	4 (7.84)		
Hilum of right lung	3 (1.95)	0 (0.00)	0 (0.00)	1 (1.56)	2 (3.92)		
Mediastinum	2 (1.30)	1 (4.00)	0 (0.00)	0 (0.00)	1 (1.96)		
TNM Staging, n (%)						4.584	0.205
II	28 (18.18)	5 (20.00)	1 (7.14)	16 (25.00)	6 (11.76)		
III	126 (81.82)	20 (80.00)	13 (92.86)	48 (75.00)	45 (88.24)		
Treatment cycle, n (%)						23.743	0.001
2	66 (42.86)	9 (36.00)	1 (7.14) [c]	36 (56.25) [c]	20 (39.22)		
3	26 (16.88)	0 (0.00)	3 (21.43)	13 (20.31)	10 (19.61)		
4	62 (40.26)	16 (64.00) [a]	10 (71.43) [c]	15 (23.44) [a,c]	21 (41.18)		

T tislelizumab treatment + chemotherapy, *S* surgery treatment, *C* chemotherapy, *NS* non-surgery treatment, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *SD* standard deviations, *LUSC* lung squamous cell carcinoma, *LUAD* lung adenocarcinoma

[a] significantly different between T+S and C+S

[b] significantly different between T+S and C+NS

[c] significantly different between T+NS and C+S

Table 2 Clinical response

Response	All (n = 154)	T (n = 39)	C (n = 115)	Test value	P-value
Clinical response, n (%)				−2.889	0.004
CR	5 (3.25)	2 (5.13)	3 (2.61)		
PR	59 (38.31)	22 (56.41)	37 (32.17)		
SD	82 (53.25)	14 (35.90)	68 (59.13)		
PD	8 (5.19)	1 (2.56)	7 (6.09)		
ORR (CR + PR), n (%)	64 (41.56)	24 (61.54)	40 (34.78)	8.584	0.003

T tislelizumab treatment + chemotherapy, *S* surgery treatment, *C* chemotherapy, *NS* non-surgery treatment, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressed disease, *ORR* objective response rate

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Table 3 Pathological response

Response	All (n = 89)	T + S (n = 25)	C + S (n = 64)	Test value	P-value
Pathological response				−3.520	< 0.001
Viable cells = 0%	19 (21.35)	10 (40.00)	9 (14.06)		
Viable cells < 10%	9 (10.11)	5 (20.00)	4 (6.25)		
Viable cells > 10%	61 (68.54)	10 (40.00)	51 (79.69)		
pCR	19 (21.35)	10 (40.00)	9 (14.06)	7.203	0.007
MPR	28 (31.46)	15 (60.00)	13 (20.31)	18.296	< 0.001

T tislelizumab treatment, *S* surgery treatment, *C* chemotherapy, *pCR* pathological complete response, *MPR* major pathological response

Table 4 Progression-free survival and overall survival analysis after adjustment

		PFS			OS	
	Median survival time (days, 95% CI)	HR (95% CI)	P-value	Median survival time (days, 95% CI)	HR (95% CI)	P-value
C + NS	369 (189–549)	Reference		603 (427–779)	Reference	
T + NS	415 (390–440)	0.668 (0.294–1.516)[a]	0.335	996 (700–1292)	0.912 (0.357–2.330)[a]	0.848
C + S	645 (548–742)	0.632 (0.386–1.036)[b]	0.069	Not reached	0.533 (0.317–0.898)[b]	0.018
T + S	Not reached	0.129 (0.045–0.373)[a,b]	< 0.001	Not reached	0.149 (0.045–0.497)[a,b]	0.002

T tislelizumab treatment + chemotherapy, *S* surgery treatment, *C* chemotherapy, *NS* non-surgery treatment, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

[a]significant difference between T+NS and T+S
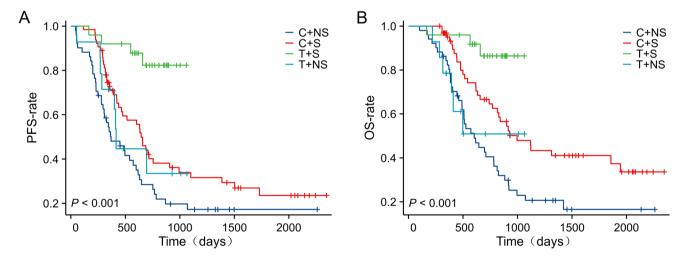
[b]significant difference between C+S and T+S

Fig. 1 Survival curves of the participants stratified by surgery or not and the utilization of tislelizumab. **A** PFS curves of the four groups; **B** OS curves of the four groups. *C* chemotherapy; *NS* non-surgery, *T* tislelizumab treatment + chemotherapy, *S* surgery treatment, *PFS* progression-free survival, *OS* overall survival

p < 0.001) and an 85.1% reduced risk of death (HR = 0.149 [95%CI: 0.045–0.497], p = 0.002). The T + S group exhibited a proportionately higher reduction in the risk of disease progression or death compared to the sum of the T + NS group and C + S group.

　　Pairwise comparisons among the four groups are summarized in Table 4, Supplementary Table 3, and Supplementary Table 4. In the pairwise comparison, regardless of the tislelizumab utilization, surgery was significantly associated with improved OS (both ps < 0.05). However, surgery was significantly associated with improved PFS (HR = 5.277, p = 0.002) only in the presence of tislelizumab. In the absence of surgery, tislelizumab utilization was not associated

with significant PFS or OS improvement. However, in the presence of surgery, tislelizumab utilization was associated with significantly improved PFS (HR = 0.224, p = 0.001) and OS (HR = 0.290, p = 0.022).

4 Discussion

This study investigated the potential synergistic effect of tislelizumab plus surgery on the survival benefit in patients with TNM stage II-III NSCLC. The results demonstrate a promising paradigm for improving treatment outcomes in this specific patient population.

In the study, regardless of the preoperative medication, surgery is associated with a significant improvement in survival, especially in preoperative tislelizumab plus chemotherapy setting. Surgery is considered the standard of care for early-stage or locally advanced NSCLC even in the era of immunotherapy. NSCLC exhibit immunosuppressive features generally [18] and accumulating evidence suggests that a high tumor burden, indicated by tumor volume, circulating free tumor DNA and/or circulating tumor cells, has a negative effect on anticancer immunity [19]. Surgery can remove a significant portion of the tumor mass. By reducing the tumor burden, immunotherapy can be more effective in targeting the residual cancer cells.

Evidence on tumor downstaging through immunochemotherapy followed by subsequent surgical treatment in initially unresectable stage III NSCLC patients remains insufficient. In this cohort, stage III patients constituted 81.82%, with an overall conversion rate of 57.8% (89/154) and 64.1% (25/39) in the tislelizumab group. For this subgroup, surgery remains a controversial option within traditional standard treatment protocols. The surgical strategy should be based on multidisciplinary discussions and patient preferences in experienced centers in applying immunotherapy in the preoperative setting. If surgical treatment is not selected, further evidence is needed to determine whether to continue with medical treatment or opt for chemoradiotherapy with diligent follow-up.

Besides, the risk of disease progression remains a challenge. In the study, the median progression-free time in C + NS group was only 369 days. Considering the potential mechanisms of tislelizumab potentiating surgical treatment efficacy on survival, tislelizumab may shrink the size of the tumor, which allows for less invasive surgical procedures, fewer surgery-related complications, and potentially improves the chances of achieving clear surgical margins. Besides, tislelizumab may have the potential to eliminate cancer cells that have already metastasized but are not detectable preoperatively, as well as residual cancer cells postoperatively, by harnessing its immunological memory function [20]. However, further studies are warranted to delve deeper into the mechanism underlying this effect.

Moreover, the safety profile of tislelizumab observed in this study was consistent with previous reports in NSCLC and other malignancies [8, 21], with even fewer adverse events compared to classical chemotherapy in some aspects. This is a crucial consideration when assessing the feasibility of combining immunotherapy with surgery, as treatment-related adverse events could potentially impact patient survival. The manageable safety profile of tislelizumab makes it a promising candidate for further investigation and potential clinical implementation.

Despite the encouraging results, several limitations need to be acknowledged in this study. The relatively small sample size and single-center nature of the research may limit the group balance and generalizability of the findings. Statistical adjustments were applied to control the group imbalance in the study. Also, larger multi-center randomized controlled trials are required to confirm the observed survival benefit. Furthermore, the long-term follow-up data are crucial to assess the durability of the treatment effect and to determine if the observed survival benefit is sustained over time. Additionally, investigating potential biomarkers predictive of response to tislelizumab plus surgery would be beneficial to identify patients who are most likely to benefit from this therapeutic strategy.

In conclusion, the current study provides compelling evidence supporting tislelizumab plus surgery as a potential treatment option for patients with stage II-III NSCLC. The observed synergistic effect and manageable safety profile make tislelizumab an attractive candidate for further investigation in larger clinical trials, offering a more effective and personalized treatment strategy.

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Data availability Data can be obtained upon request and should be directed toward the corresponding author. Data cannot be made freely available in a public repository due to restrictions based on privacy regulations and the informed consent of the participants.

Declarations

Competing interest The authors declare no competing interests.

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